Vascular arteritides in women

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The vasculitides are multiple clinical disease states that are characterized by inflammation of the wall of blood vessels. They are typically classified by the size of the vessel that is affected. Some of the vasculitides are more commonly identified in women, such as the large-vessel vasculitides. In addition, the incidence of some of the medium and small-vessel vasculitides in women has increased during the past several decades. These inflammatory conditions specifically affecting women will be reviewed here. The implications that pregnancy may have on various vasculitides will also be highlighted. (J Vasc Surg 2013;57:27S-36S.)

Vasculitides are a group of disorders that are characterized by inflammation and tissue necrosis within the wall of a blood vessel. It is this inflammatory process that leads to symptoms, most often due to stenosis or occlusion of the vessel lumen. Vasculitides are categorized as primary, for which there is most often an unknown etiology, or secondary, in which there is typically an underlying disease or trigger that can be identified. Primary vasculitides are further classified by the size of the vessel involved, with subgroups being those with large vessel involvement, such as the aorta and its branches, medium vessel involvement, or small-vessel involvement.

Some vasculitides are more commonly identified in women, such as giant cell arteritis (GCA) and Takayasu arteritis (TA). In addition, fibromuscular dysplasia (FMD) is a disease that mimics vasculitis and is more common in women. Many of the vasculitides in medium and small vessels have been historically more prevalent in men. However, polyarteritis nodosa (PAN), Wegener granulomatosis (WG), and thromboangiitis obliterans (TAO), otherwise known as Buerger disease, have seen an increase in the overall percentage of women affected. This review will highlight those vasculitides that are most prevalent in women as well as those that demonstrate a trend toward an increase in women. Vasculitis in pregnancy is an issue that will also be reviewed.

LARGE-VESSEL VASCULITIDES

GCA. GCA, also known as temporal arteritis, predominantly affects patients aged >50 years. It is the most common vasculitis affecting Caucasians. Similar to other autoimmune diseases, GCA affects women at a 2.5-fold to 3-fold higher rate than men. The mean age of onset of symptoms is 70 years.[1,2] With respect to epidemiology, there is a positive correlation between latitude and incidence. Various organisms have been postulated to trigger GCA; to date, however, no infectious etiology has been definitively linked to development of the disease.[3]

The pathologic hallmark of the disease is granulomatous inflammation of the medium and large vessels. The media is the most frequently affected layer, although all three layers can be inflamed. The inflammation most often occurs in the superficial temporal, ophthalmic, and vertebral arteries. The most common symptom seen with the disease is headache, affecting 60%. The most severe complications of the disease are optic neuropathies, with resultant vision loss and ischemic stroke. These complications are due to intimal proliferation and occlusion rather than thrombosis.[4] Although risk factors for these catastrophic events have yet to be defined, elevated platelet counts, jaw claudication, and amaurosis fugax are all reported risk factors for permanent visual loss.[5,6] These patients also have higher rates of aortic involvement, occurring in 15% of GCA patients as a late manifestation of the disease.[7-9]

A temporal artery biopsy specimen is the gold standard for diagnosis. The presence of giant cells has been shown to correlate with intimal proliferation. Corticosteroids are the treatment of choice for the disease. Usually, prednisolone is given at doses of 40 to 80 mg/d for 1 month and then tapered to 20 mg/d as a maintenance dose. Two randomized controlled trials have been conducted to compare methotrexate with corticosteroids, each arriving at opposite conclusions.[10,11]

TA. TA is a large-vessel vasculitis affecting the aorta and its primary branches and may lead to arterial segmental stenosis, occlusion, or aneurysm formation. This disease is significantly more predominant in women, with a female-to-male ratio of 8:1.[12-14] In contrast to GCA, TA is a disease of younger people, with age <40 years being one of the classification criteria for the condition.[2,15] The American College of Rheumatology has identified six major criteria for the diagnosis of this disorder. (Table I). The presence of three or more of these criteria is needed for diagnosis. Small subsets of patients experience a self-limiting

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Table I. Diagnostic criteria for the diagnosis of Takayasu arteritis (*TA*)[a,b]

1.	Development of symptoms before the age of 40 years.
2.	Claudication of the upper extremities.
3.	Decreased brachial artery pulse.
4.	Blood pressure difference of >10 mm Hg between arms.
5.	Bruit in subclavian artery.
6.	Angiographic evidence of narrowing or occlusion of the aorta, primary branches, or large arteries in the proximal upper or lower extremities not due to atherosclerosis or FMD.

FMD, Fibromuscular dysplasia.
[a]If at least three of these criteria are present, the diagnosis of TA can be made with a sensitivity of 90.5% and specificity of 97.8%.
[b]Criteria are based on the American College of Rheumatology 1990 Guidelines.

inflammatory episode that does not progress or require lifelong therapy; however, predicting this subset of patients is not currently possible. Visual disturbances (10%), as well as transient ischemic attack (20%) and stroke (5%) are known to occur in these patients.[4] Although most lesions occur in the proximal segments of arteries arising from the transverse aortic arch, the incidence of aortic valve regurgitation is 13% to 25%. Many patients respond to corticosteroids; however, relapses or steroid dependence often necessitates the use of combination therapy with azathioprine and methotrexate.[16-20]

Patients with TA are challenging with regard to the selection of appropriate surgical candidates and in the technical aspects of the operation. Although medical management of acute disease and delayed surgical intervention until acute inflammation has subsided is preferable, urgent neurologic symptoms or uncontrolled hypertension may prompt operative intervention. Surgery for brachiocephalic trunk disease is infrequently necessary and limited to these with neurologic symptoms, severe upper extremity claudication, and occasionally, those with severe bilateral carotid stenosis.[9,20,21] In addition, aortic and renal procedures may be required for extreme cases of uncontrolled hypertension.[22,23] Splanchnic vessel involvement is uncommon; however, patients with visceral ischemia may require surgical intervention.

FMD. FMD is considered a disease of children and young women of childbearing age and is the most common cause for secondary hypertension in this population.[9,24,25] Of patients with identified FMD, renal involvement occurs in 60% to 75%, cerebrovascular involvement occurs in 25% to 30%, visceral involvement occurs in 9%, and arteries of the limbs are affected in ~5%.[26] Disease is found in more than one arterial region in 26% of patients. Women aged 20 to 60 years are the most commonly affected group and often present with recalcitrant hypertension.

There are three main types of renal artery FMD (RAFMD). Medial fibroplasia is the most common type, accounting for 80% of cases.[27,28] Bilateral RA involvement occurs in one-third of patients.[29] The disease is rarely associated with loss of renal function, although progression of stenosis has been shown to occur in 37%.[24,25,30] Diagnostic angiography remains the gold standard for diagnosis. The characteristic "string-of-beads" appearance on angiography is associated with the medial type of RAFMD, whereas focal narrowing is seen with the intimal type of RAFMD.[28,31,32] Recent technologic advances, specifically the use of intravascular ultrasound imaging, have significantly improved the diagnosis and treatment of the disease. Intravascular ultrasound imaging allows for accurate sizing of the balloons as well as an accurate assessment of the severity of stenosis.[32] When treatment is recommended for patients with recurrent hypertension or worsening renal function, endovascular therapy with balloon angioplasty is the preferred modality. Technical success rates of 100% have been reported; however, clinical success rates, defined as improvement of hypertension, are much lower, ranging from 21% to 72%. Accurate balloon sizing, without oversizing, is crucial for prevention of rupture during angioplasty.

Cerebrovascular FMD is the second most common location for FMD and is predominantly a disease of women, occurring at a ratio of approximately 3:1 to 4:1.[25] In those patients with cerebrovascular FMD, the internal carotid artery is most often involved (95%), usually at the C1-C2 level.[33] In an additional one-third, the vertebral artery is involved. Cerebrovascular FMD is frequently associated with intracranial aneurysms, and although the link between FMD and aneurysms is not well defined, the reason for this phenomenon is possibly related to an underlying connective tissue problem that results in loss of arterial wall strength.[25,28] FMD is an important cause of stroke in young adults, especially young women. Most patients with craniocervical FMD are asymptomatic. Others report nonspecific problems such as headache, lightheadedness, vertigo, and tinnitus. Neck pain may be an initial presenting symptom in patients with arterial dissection. The symptoms of stroke can be varied but most often involve the anterior circulation. The gold standard for diagnosis is conventional angiography. Similar to renal FMD, lesions typically show a beading pattern on angiography. Four-vessel angiography should always be performed because of the high incidence of multiple vessel involvement.

The treatment of choice for uncomplicated cerebrovascular FMD is antiplatelet therapy. Percutaneous angioplasty is the standard treatment for symptomatic cerebrovascular FMD. Stents are used only when dissection occurs and is symptomatic.[32] If arterial dissection is identified and is asymptomatic, then anticoagulation is the treatment of choice. This has not been well studied; however, based on limited literature, anticoagulation therapy should continue for 3 to 6 months. Some neurologists advocate the use computed tomography angiography or magnetic resonance angiography to reassess of the arteries before discontinuation of anticoagulation. Other groups have recommended antiplatelet therapy continue indefinitely.[32]

Table II. Criteria for the diagnosis of polyarteritis nodosa (PAN)

1.	Weight loss >4 kg: Loss of >4 kg body weight since illness began, not related to dieting or other factors.
2.	Livedo reticularis: Mottled reticular pattern over the skin of portions of the extremities or torso.
3.	Testicular pain/tenderness: Pain or tenderness of the testicles, not due to infection, trauma, or other causes.
4.	Myalgias, weakness, or leg tenderness: Diffuse myalgias (excluding shoulder or hip girdle) or weakness of muscles or tenderness of leg muscles.
5.	Mononeuropathy or polyneuropathy: Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy.
6.	Diastolic blood pressure >90 mm Hg: Development of hypertension with the diastolic blood pressure >90 mm Hg.
7.	Elevated blood urea nitrogen or creatinine: Elevation of blood urea nitrogen >40 mg/dL or creatinine >1.5 mg/dL, not due to dehydration or obstruction.
8.	Arteriographic abnormality: Arteriogram showing aneurysms or occlusions of the visceral arteries, not due to arteriosclerosis, FMD, or other noninflammatory causes.
9.	Hepatitis B virus: Presence of hepatitis B surface antigen or antibody in serum.
10.	Biopsy specimen of small or medium-sized artery containing polymorphonuclear cells: Histologic changes showing the presence of granulocytes or granulocytes and mononuclear leukocytes in the artery wall.

FMD, Fibromuscular dysplasia.

MEDIUM-VESSEL VASCULITIDES

PAN. PAN was first described in 1866 by Kussmaul and Maier,[34] who noted arterial nodules during the autopsy of a patient who had presented with systemic symptoms. The 1994 Chapel Hill Consensus Conference defined PAN as necrotizing inflammation of medium or small arteries in the absence of glomerulonephritis or vasculitis in arterioles, capillaries, or venules.[35] Classically, men are affected twice as often as women, with the onset on symptoms in the fifth to sixth decades of life.[36] However, a recent series from Lugo, Spain, noted that men did not predominate in their population of patients and that the disease may also have a later onset in women.[37] PAN is generally idiopathic, although an association with hepatitis B infection (HBV) has been established. Several cases of presumed HBV vaccine–associated vasculitis, thought to potentially represent immune complex disease, have been reported to the Vaccine Adverse Event Reporting System (VAERS).[38]

The American College of Rheumatology 1990 criteria for the classification of PAN reported a sensitivity of 82.2% and specificity of 86% in distinguishing PAN from other vasculitides. According to these criteria, vasculitis should be classified as PAN if at least three of 10 specified criteria are present[39] (Table II). As suggested by these criteria, systemic symptoms, such as fever, weight loss, myalgias, and arthralgias are common, as are neurologic manifestations, including peripheral neuropathy or mononeuritis multiplex. Serious renal and gastrointestinal complications are less common but are associated with a poor prognosis. Cardiovascular involvement may range from cardiomyopathy to digital ischemia. Classic vascular findings include multiple visceral aneurysms. Peripheral, coronary, intracranial, and end-organ (renal, hepatic) aneurysms have also been reported.[40] The erythrocyte sedimentation rate may also be markedly elevated. Perinuclear antineutrophilic cytoplasmic antibodies may be present. Other laboratory findings may demonstrate end-organ effects, such as renal dysfunction.[41]

Corticosteroids are first-line therapy in the treatment of PAN, with the addition of cyclophosphamide in severe or refractory cases and with the addition of antiviral agents and possibly plasma exchange for HBV-associated PAN.[42] Anti-tumor necrosis factor agents and intravenous immunoglobulin infusions remain investigational. Aneurysms may be treated as needed by open ligation with or without revascularization or, as is becoming more common, with endovascular modalities such as embolization or stent graft exclusion.[41,43,44]

SMALL-VESSEL VASCULITIDES

The antineutrophil cytoplasmic autoantibody-associated vasculitides. WG, Churg-Strauss syndrome (CSS), and microscopic polyangiitis (MPA) typically affect small vessels and are collectively known as antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides, or AAVs. The Chapel Hill Consensus Conference presented a system of nomenclature in 1994 to establish uniform definitions for PAN and the AAVs[35] (Table III). There has been a recent move to substitute "granulomatosis with polyangiitis" for WG, driven by a general desire to move from eponyms to pathology-based terminology but also influenced by growing controversy surrounding Dr Wegener's association with the Nazi regime before and during World War II. Under a pathology-based terminology, CSS is identified as eosinophilic granulomatosis with polyangiitis.[45,46]

The ANCA-associated vasculitides continue to be considered primary, idiopathic entities. However, epidemiologic studies have identified potential geographic, ethnic, genetic, environmental, occupational, and infectious associations, suggesting multifactorial contributions to the development of disease.[47] The overall annual incidence of PAN and AAVs is estimated at between 10 and 20 cases/million population. Available data are skewed by the predominance of white, European populations (United Kingdom, Australia, Spain, Sweden, Finland, Norway, and United States) in the research populations and the paucity of data regarding African, South Asian, and other non-Western groups.[47]

WG is a systemic, necrotizing small-vessel vasculitis. The initial case was reported by Klinger in 1931; however, Friedrich Wegener ultimately characterized the disease through clear delineation of the clinical and pathologic

Table III. Definitions of vasculitides[a]

1.	Polyarteritis nodosa (PAN): Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules.
2.	Wegener granulomatosis (WG): Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small-sized to medium-sized vessels (eg, capillaries, venules, arterioles, and arteries). Necrotizing glomerulonephritis is common.
3.	Churg-Strauss syndrome (CSS): Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small-sized to medium-sized vessels and associated with asthma and blood eosinophilia.
4.	Microscopic polyangiitis (MSA): Necrotizing vasculitis with few or no immune deposits affecting small vessels (ie, capillaries, venules, or arterioles). Necrotizing arteritis of small-sized and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.

[a]Chapel Hill Consensus Conference on the nomenclature of systemic vasculitis.

features several years later in 1936. Typically, WG has been documented to equally affect both men and women, or even to be slightly male-predominant.[48,49] However, the study from Lugo, Spain, observed a higher incidence in women, much like that seen in PAN in that population of patients.[50] A group of North American patients were also noted to have a slightly increased prevalence in women (56%), as in the Spanish cohort, with this group of patients presenting with an earlier onset (age, 9-40 years).[51]

The Chapel Hill Consensus Conference definitions do not constitute diagnostic criteria, leaving clinicians to rely largely on the American College of Rheumatology's 1990 diagnostic criteria for PAN, CSS, and WG[39,52,53] (Tables IV and V). Because the application of these criteria creates a great deal of overlap among PAN and the AAVs, a stepwise algorithm has been created for the classification of these vasculitides.[54] Immunologically, perinuclear ANCA is characteristic of CSS and MPA, whereas cytoplasmic ANCA is typically associated with WG. Histologic features may also aid in distinguishing among the AAVs. Eosinophilia is a prominent feature of CSS, as reflected in the proposed pathology-based nomenclature, and is apparent in the white blood cell differential and in biopsy specimens.

Clinically, respiratory symptoms predominate in CSS, from asthma to pulmonary infiltrates and sinus symptoms. ANCA status may affect presentation: the French Vasculitis Study Group found that ANCA-positive CSS patients were more likely to have renal and neurologic disease, whereas the ANCA-negative group demonstrated more frequent cardiac involvement.[55] MPA was once considered a microscopic form of PAN and currently lacks its own set of ACR diagnostic criteria. Many now consider MPA to be part of the clinical spectrum of WG, without the granulomatous histologic findings typical of that entity. Renal and pulmonary involvement is common in MPA.

The mainstay of treatment of AAV is immunosuppression. The initial focus is induction of remission, most commonly with corticosteroids and oral cyclophosphamide. Remission may be maintained with a reduced dose of corticosteroids and, potentially, with alternatives to cyclophosphamide such as azathioprine, methotrexate, or mycophenolate mofetil.[56] Therapeutic agents under investigation, primarily for the treatment of refractory disease, include antitumor necrosis factor agents, such as etanercept or infliximab, rituximab (anti-CD20 monoclonal antibody), and intravenous immunoglobulin.[57]

Table IV. Criteria for the classification of Wegener granulomatosis (WG)[a,b,c]

1.	Nasal or oral inflammation: Development of painful or painless oral ulcers or purulent or bloody nasal discharge.
2.	Abnormal chest radiograph: Chest radiograph shows the presence of nodules, fixed infiltrates, or cavities.
3.	Urinary sediment: Microhematuria (>5 red blood cells per high-power field) or red cell casts in urine sediment.
4.	Granulomatous inflammation on biopsy specimen: Histologic changes show granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (artery or arteriole).

[a]Need two of four criteria for diagnosis. The presence of any two or more criteria yields a sensitivity of 88.2% and a specificity of 92.0%.
[b]American College of Rheumatology 1990 criteria.
[c]Leavitt et al.[53]

ANCA measurements are important in establishing the diagnosis of AAV but are of limited utility in predicting relapse or tracking the course of disease.[58] Several instruments have been developed to formalize the clinical assessment of disease activity and severity in order to guide optimal therapy. These include the Birmingham Vasculitis Activity Score for all AAVs, the Birmingham Vasculitis Activity Score for WG and the Disease Extent Index to assess WG, and the Vascular Damage Index and ANCA-associated Vasculitis Index of Damage to quantify end-organ damage.[59] Also appropriate are system-specific investigations, such as urine studies and serum creatinine to assess renal dysfunction, chest radiography to assess pulmonary disease, nerve conduction studies for peripheral neuropathy, or echocardiography to assess myocardial or valvular dysfunction.

Patients with AAVs may be more prone to thrombotic or thromboembolic events, whether as a consequence of vessel damage or of prothrombotic factors. An increased incidence of venous thrombotic events was recently observed among patients with WG.[60]

TAO. TAO, also referred to as Buerger disease, is a segmental, nonatherosclerotic inflammatory disorder. It is classified under vasculitis of the medium vessels because it primarily affects the medium and small vessels. TAO was initially described by Von Winiwarter in 1879.

Table V. Criteria for the classification of Churg-Strauss syndrome (*CSS*)[a,b,c]

1.	Asthma: History of wheezing or diffuse high-pitched expiratory rhonchi.
2.	Eosinophilia: Eosinophilia >10% on differential white blood cell count.
3.	Mononeuropathy or polyneuropathy: Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy (glove/stocking distribution) attributable to systemic vasculitis.
4.	Pulmonary infiltrates, nonfixed: Migratory or transitory pulmonary infiltrates (not including fixed infiltrates) due to vasculitis.
5.	Paranasal sinus abnormality: History of acute or chronic paranasal sinus pain or tenderness or radiographic opacification of the paranasal sinuses.
6.	Extravascular eosinophils: Biopsy specimen including artery, arteriole, or venule showing accumulations of eosinophils in extravascular areas.

[a]Classified as CSS if at least four of six criteria are present.
[b]American College of Rheumatology 1990 criteria.
[c]Masi et al.[52]

However, Leo Buerger formally published a detailed description of the pathologic alterations associated with the disease, which he studied from the vessels of amputated limbs in 1908.

The annual incidence of TAO in the United States was reported as 12.6 persons/100,000 in 1986, which has decreased from the incidence of 104 persons/100,000 noted in 1947.[61] TAO is most prevalent in patients who are of Middle Eastern and Far Eastern origin. The prototypical patient is a man with a history of tobacco use, usually aged <45 years. However, the disease may also be seen in women, and in addition, an increase in the incidence of TAO in women has been noted. Several studies have reported an increase in the prevalence of the disease in women ranging from 11% to 23%.[61] Interestingly, the prevalence of TAO in Asian women with a history of tobacco use is quite low.[62] Historically, between 1964 and 1970, the rate of TAO in women in one series was 5%. Between the years 1970 and 1995, it rose to 9.3%. From 1995 to 2001, it remained relatively stable, at 9.8%.[63] Sasaki et al[64] demonstrated that the age at initial diagnosis was higher in women than in men (42.9 vs 39.8 years).

The cause of TAO remains largely unknown, although the use of tobacco clearly plays a central role in the disease process and progression.[65] Numerous studies have identified an extremely strong association between tobacco use and TAO, and many clinicians believe that smoking (either currently smoking or a history of smoking) is a mandatory clinical factor for diagnosis.[66] There is also strong evidence of a cell-mediated immune response affecting arteries and veins. In the acute phase, this is characterized by inflammatory infiltration of the internal elastic lamina, with a transition in the cellular composition of this response in the chronic phase. The role of ANCA, antiendothelial cell antibodies, and antielastin antibodies is also being investigated, as is an apparent association of TAO with the presence of the prothrombotic *G20210A* prothrombin gene mutation. Ultimately, the impairment in endothelial-dependent relaxation of the peripheral vessels and other typical findings of TAO appear to result from a multifactorial etiology resulting from the interplay of environmental, hereditary, and immune factors.[67]

Several sets of criteria have been developed for the diagnosis of TAO. Shionoya's[68] criteria include (1) smoking history; (2) onset of symptoms before age 50 years; (3) infrapopliteal arterial occlusions; (4) either arm involvement or phlebitis migrans; and (5) absence of atherosclerotic risk factors other than smoking. Olin's[61] criteria include (1) age <45 years; (2) present or recent history of tobacco use; (3) presence of distal extremity ischemia (claudication, pain at rest, ischemic ulcers or gangrene) documented by noninvasive vascular testing; (4) exclusion of autoimmune diseases, hypercoagulable states, and diabetes mellitus; (5) exclusion of a proximal source of emboli by echocardiography or arteriography; and (6) consistent arteriographic findings in the clinically involved and noninvolved limbs. The scoring system proposed by Papa and Adar[66] assigns points to positive and negative criteria and defines the diagnosis as definite if 6 or more points are present, probable if 4 to 5, suspected if 2 to 3, and excluded if ≤1.

Typical arteriographic lesions are described as corkscrew-shaped collaterals, known as Martorell's sign, which may represent compensatory changes in vasa vasorum, in the presence of segmental lesions, or in occlusions in the distal extremity. Although the distal extremities are typically affected, there are rare reports of visceral, renal, aortoiliac, and intracranial manifestations.[67] Ischemic pain and tissue loss present a significant challenge in this population.

Smoking cessation is significantly associated with a reduced risk of amputation. Interestingly, however, an equivalent benefit may not be achieved in long-term survival, which in one large study appeared to remain significantly lower than expected despite this intervention.[69] Pharmacotherapy has largely been limited to the generalized recommendation of antiplatelet therapy and the use, in Europe, of prostanoids, most notably intravenous iloprost, which may offer pain relief benefits. There are mixed data on the benefit of iloprost for ulcer healing. Several studies have also suggested that bosentan, an oral endothelin receptor antagonist, may be of benefit.[70]

Owing to the very distal nature of the occlusive lesions, reconstruction is frequently not possible. If technically feasible, however, revascularization may, even with limited patency, be helpful in healing ischemic lesions. The role of open, laparoscopic, thoracoscopic, or chemical lumbar or cervicothoracic sympathectomy in the treatment of refractory ischemic pain and nonhealing ulcers is controversial. There are positive and negative reports in the literature on the presence of clinical benefit with regard to pain control or wound healing. At least one study of microcirculation in TAO patients failed to show an immediate improvement in lower extremity microcirculation after

lumbar sympathectomy.[71] The use of omental pedicle flaps has also been reported.[72] Several reports of clinical improvement with the use of implantable spinal cord stimulators have also been published.[73]

Raynaud's phenomenon. Primary and secondary Raynaud's phenomenon (RP) are the favored terms for the group of vasospastic phenomena previously known, respectively, as Raynaud's disease, denoting primary, idiopathic vasospastic digital ischemia, or Raynaud's phenomenon, which typically referred to digital vasospasm secondary to other disorders[74] (Table VI). The classic presentation is that of digital ischemia associated with excessive sympathetic activation and linked with triggers such as cold or emotional distress. Although the documented prevalence of primary RP varies widely among geographic and ethnic populations, it is consistently more common in women. The gender prevalence is much more marked in white than in African American or Asian populations. The degree of variation has been proposed to reflect differences based on ethnicity, climate, and diagnostic methodology.[74] Secondary RP does not, per se, carry a gender association, but it is quite common in several disorders, such as scleroderma and systemic lupus erythematosus, that disproportionately affect women. Erythromelalgia and acrocyanosis are, like RP, functional vascular disorders. Erythromelalgia manifests as painful, paroxysmal burning pain of the feet or hands associated with color changes and, occasionally, even tissue loss. Acrocyanosis presents as painless, bilateral, dusky discoloration of the hands and feet. Both, like RP, affect women significantly more frequently than men.[75]

The pathophysiology of RP is that of enhanced vasoconstriction, impaired vasodilation, and modulation of the adrenoreceptor response. The sympathetic component is mediated by norepinephrine and stimulation of α-2 receptors. There may be modulation of α-1 and α-2 receptor responses in RP. Vasoconstriction is further favored by increased endothelin-1 activity in these patients and, potentially, increased activity of vasoconstrictor cyclooxygenase factors, such as prostaglandins and thromboxane, and an altered response to 5-hydroxytryptophan. Similarly, there appears to be impairment of vasodilation through nitric oxide-mediated pathways and other pathways.[76]

The diagnosis of primary RP is one of exclusion: the typical episodic attacks of digital ischemia must be present without any physical examination or laboratory evidence of secondary causes[77] (Table VII). A history of digital ischemia combined with the presence of any of the factors associated with secondary RP is strongly suggestive of that diagnosis; otherwise, primary RP may be diagnosed. Younger age and female gender are typically associated with primary RP. The physical examination may suggest a prominent subclavian pulse suggestive of arterial thoracic syndrome, which may result in aneurysm formation and distal emboli, as well as evidence of occlusive disease of the more distal arteries. Examination of the hands may demonstrate evidence of emboli or connective tissue disease, both suggesting secondary RP. Capillary microscopy, if abnormal, also suggests secondary RP associated with scleroderma/systemic sclerosis.[78] Special note should be taken of evidence of active or healed ulcers.

Noninvasive vascular studies offer an assessment of the presence and level of upper extremity arterial occlusive disease. Finger pressures, particularly in conjunction with the use of a cold challenge test involving assessment of recovery after cold (4°C) water immersion, are also useful in establishing the diagnosis of RP.

Primary and secondary RP demonstrate a substantially different natural history. Whereas primary RP is typified by a benign course that rarely progresses to tissue loss and by relatively frequent spontaneous remission, secondary RP is more commonly progressive over time and associated with significant complications. The initial management of primary and uncomplicated secondary RP includes risk factor modification: avoiding cold exposure, emotional stress, and other possible environmental triggers such as smoking or caffeine. Medications associated with vasospasm or secondary RP should, if possible, be discontinued. Biofeedback, aimed at developing learned control of autonomic functions to increase skin perfusion, appears to benefit a subset of primary RP patients.

First-line pharmacologic treatment consists of dihydropyridine calcium-channel blockers, of which nifedipine is the most widely used. Oral or topical preparations of nitroglycerin have also been used effectively. Losartan, an angiotensin II receptor antagonist, has shown benefit, as has prazosin, an α-1–adrenergic blocker. For more severe or refractory disease, intravenous infusion of the prostaglandin iloprost has been associated with reduced attack severity, duration, and frequency, as well as improved ulcer healing. Bosentan, an oral endothelin receptor antagonist, has shown benefit in several European studies in the prevention of new digital ulcers and healing of existing ulcers in patients with RP secondary to systemic sclerosis. Several studies have also suggested symptomatic improvement or improved ulcer healing with the use of the phosphodiesterase type 5 inhibitors sildenafil, tadalafil, and vardenafil. The potential role of serotonin receptor antagonists, serotonin reuptake inhibitors, and antioxidants, such as *N*-acetylcysteine, is under investigation.[79]

Several interventional therapies for severe RP aim to directly disrupt the neural pathways involved in vasospasm. These range from open or surgical lumbar or cervicothoracic, digital, or chemical sympathectomy to interdigital injection of botulinum toxin-A. The role of lumbar or cervicothoracic sympathectomy remains controversial, because reported results are inconsistent and benefits may not prove durable over time. Surgical sympathectomy is generally reserved for severe, refractory cases.[80-82] Implantable spinal cord stimulators have also shown promise in managing ischemic pain associated with severe RP.[83,84]

VASCULITIS IN PREGNANCY

Although uncommon, vasculitis in pregnancy is an important topic because several of the above-mentioned vasculitides may occur with some frequency during the childbearing years. To achieve an uncomplicated

Table VI. Conditions associated with secondary Raynaud's phenomenon (RP)

1.	Connective tissue diseases: Scleroderma, rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disease, dermatomyositis, small- and medium-vessel vasculitis.
2.	Arterial occlusive disease: Atherosclerotic arterial occlusive disease, TAO (Buerger disease), embolic disease.
3.	Hematologic: malignancy (multiple myeloma, adenocarcinoma, leukemia, astrocytoma), polycythemia vera, cryoglobulinemia, cold agglutinin disease.
4.	Drug-induced: β-blockers, clonidine, ergot alkaloids, chemotherapeutic agents (bleomycin, vinca alkaloids, cisplatin, interferon-α), drugs of abuse (cocaine, amphetamine), nicotine.
5.	Traumatic: vibrational arteriopathy, hypothenar hammer syndrome, thoracic outlet syndrome (neurogenic or arterial), carpal tunnel syndrome.

TAO, Thromboangiitis obliterans.

pregnancy, women with primary vasculitides should be advised to plan for conception when their disease is inactive. The prepregnancy goal is to induce and maintain remission throughout the pregnancy. It is also critical to identify remission early when it does occur and treat with the least toxic pharmaceutic agent. Many of the drugs used to treat the vasculitides are toxic and may be teratogenic to the fetus. In addition, many patients with vasculitis have an increased risk of thromboembolic events, as does the state of pregnancy itself. Thus, the main objectives when treating a pregnant woman with vasculitis would include prepregnancy counseling, careful evaluation and treatment of the vasculitis, and assessment of thrombotic risk throughout the pregnancy.

Unfortunately, there is a paucity of data regarding vasculitides and pregnancy and outcomes. This is because vasculitides occur more commonly in men or in women beyond their reproductive period.[85] The limited literature available regarding treatment of specific vasculitides during pregnancy is discussed below.

TA. Because TA typically does affect women during the childbearing years, most of the large volume data on pregnancy and vasculitis focuses on TA.[86] Recommendations for patients with TA include that patients be in remission before conception, because the overall maternal and fetal outcomes are affected adversely in patients with active disease. A review of six case series found an overall 15% risk of abortion, and 8% of newborns were premature, with 15% having low birth weight.[87] Pregnancy outcome has been noted to be adversely affected by several factors, including active disease during early pregnancy, hypertension in the late gestational period, aortic or renal involvement, and a delay in medical attention.[88] Disease activity should be monitored closely in a clinical manner and with imaging, such as magnetic resonance imaging, as needed. Several studies have noted that preeclampsia occurred in nearly 40% to 50% of patients and, when present, conferred higher maternal and fetal risk. Close monitoring of blood pressure is critical when patients are in labor because the risk of intracranial hemorrhage may be increased during this time. Corticosteroids are the first line of treatment, followed by the least cytotoxic agent, such as azathioprine, should this fail.

WG. WG typically does not affect women of childbearing age. The first case of WG during pregnancy was described in 1970, and 42 pregnancies had been reported in 33 patients as of 2010.[89,90] The influence that WG may have on pregnancy seems to be unpredictable and related to the trimester when the symptoms first occur. Diagnosis should be based on clinical presentation, imaging studies, and results of serologic analysis. Although WG most commonly manifests clinically with symptoms related to the upper airway, lungs, and kidneys, some patients with WG have presented with digital ischemia.[91] Relapse in pregnancy may be life-threatening and requires aggressive medical management. As mentioned previously, prognosis in patients with WG has greatly improved through the combination of steroids and cyclophosphamide.[49] Although the use of cyclophosphamide during pregnancy has never been formally investigated, a few case reports have documented an increase in the incidence of spontaneous abortions as well as birth defects, which become accentuated when this cytotoxic agent is used in the first trimester.[92,93] When cyclophosphamide is used after the first trimester, however, the data suggest that fetal tolerance improves significantly.[94-96] Often, intravenous immunoglobulin may be used for patients presenting with WG in the first trimester or for the maintenance of remission throughout pregnancy.[97]

Table VII. Criteria for the diagnosis of primary Raynaud's phenomenon (RP)[a]

1.	Vasospastic attacks precipitated by cold or emotional stress.
2.	Symmetric attacks involving both hands.
3.	Absence of tissue necrosis or gangrene.
4.	No history or physical findings suggestive of a secondary cause.
5.	Normal nail-fold capillaries.
6.	Normal erythrocyte sedimentation rate.
7.	Negative serologic findings, particularly negative test for antinuclear antibodies.

[a]LeRoy et al.[77]

CSS. CSS may affect women of childbearing age; however, little has been published regarding pregnancy and CSS. Several case reports suggest that respiratory and cardiac symptoms present in 25% to 50% of pregnant patients. Most often, patients experience asthma. However, cardiac damage may be sufficiently severe as well as irreversible and can necessitate heart transplantation. Despite this, 67% to 80% of infants born to mothers with CSS were

healthy. Obviously, patients with CCS-related severe cardiac involvement had the poorest outcomes.[98] Treatment of CSS in pregnancy ranges from monotherapy with corticosteroids to the addition of intravenous immunoglobulin or a cytotoxic agent, such as cyclophosphamide.

PAN. The incidence of PAN tends to peak in the fifth decade; thus, there is a paucity of literature on PAN in pregnant women. However, the few case reports available indicate that patients who have been diagnosed with PAN before pregnancy and remain in remission throughout pregnancy seem to have fewer adverse events. Conversely, gravid patients with newly diagnosed PAN during pregnancy have higher rates of maternal death due to renal failure, gastrointestinal hemorrhage, respiratory failure, and coma.[99] Life-threatening disease requires treatment with cytotoxic agents in combination with corticosteroids.

The overall tenet in the management of women who present with or experience a relapse of vasculitis is early diagnosis and treatment with the least toxic agent appropriate to effectively treat the mother and protect the fetus.

CONCLUSIONS

Vasculitis in women is an issue that requires a multidisciplinary approach to manage effectively. And interestingly, several large studies have noted a rise in the incidence of vasculitides in women during the last several decades. Because some of the vasculitides presented here require surgical or endovascular management at some point in the disease process and may present with some type of ischemia, it is critical for the vascular surgeon to be familiar with these entities and their overall management.

AUTHOR CONTRIBUTIONS

Conception and design: KG, SS
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